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Cerebro-Costo-Mandibular Syndrome

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We describe two boys with the cerebro-costo-mandibular syndrome (CCMS). Both patients presented with Pierre Robin anomaly and respiratory insufficiency and died 12 hours and 10 months after birth. The first boy had muscular hypotonia, severe micrognathia, glossoptosis, short palate, preauricular tag, paraumbilical fibroma, and a small and narrow thorax. His chest roentgenographs showed marked hypoplasia of the first to tenth rib, multiple posterior rib-gaps in the only four ossified ribs. Tracheomalacia and stenosis of the left ureter was observed during autopsy. No structural cerebral anomalies were observed. Respiratory distress necessitated a tracheostomy in the second boy. He had severe micrognathia with glossoptosis and a cleft soft palate were noted. His chest roentgenograph showed a bell-shaped, small thorax with multiple dorsal rib-gap defects.

CCMS is a rare disorder often associated with Pierre Robin anomaly. Chest roentgenographs show the typical posterior rib-gap defects, which are quite variable. CCMS usually occurs as an isolated event in a family. Of 41 reported families four reports describe horizontal and two describe vertical transmission of CCMS. This might imply genetic heterogeneity with autosomal recessive and autosomal dominant inheritance. Inter- and intrafamilial expression is variable. Careful family studies are necessary before genetic counseling is given.

KEY WORDS: cerebro-costo-mandibular syndrome, Pierre Robin anomaly, rib-gap defects, severe micrognathia

INTRODUCTION

Cerebro-costo-mandibular syndrome (CCMS) is a rare disorder. Forty-eight cases [Burton and Oestreich, 1988; Caffey, 1973; Clarke and Nguyen, 1985; Drossou-Agakidou et al., 1991; Fauré et al., 1978; Feldman and Heyman, 1987; Fidalgo Alvarez et al., 1988; Gürgey et al., 1985; Harris and Fellows, 1977; Hennekam et al., 1985; Kang et al., 1992; Kemperdick and Lemburg, 1976; Kringelbach and Henriksen, 1968; Kuhn et al., 1975; Langer Jr. and Herrmann, 1974; Leroy JG et al., 1981; Lim and Koh, 1992l; McNicholl et al., 1970; Meineke et al., 1987; Merlob et al., 1987; Miller et al., 1972; Mohan and Mandalam, 1982; Nicholls and Fletcher, 1973; Schroer and Meyer, 1985; Silverman et al., 1980; Simma et al., 1989; Smith et al., 1966; Smith and Sekar, 1985; Tachibana et al., 1980; Trautman et al., 1985; Walizadeh, 1978; Williams and Sane, 1976] have been reported to date. Severe micrognathia and posterior rib-gap defects on chest roentgenographs are constant findings. Patients mostly present shortly after birth with severe respiratory insufficiency and flail chest. Pierre Robin anomaly is frequent in CCMS. In the absence of chest roentgenographs the diagnosis can be missed. We present two isolated patients with CCMS who presented with Pierre Robin anomaly and respiratory problems and review the literature.

CLINICAL REPORTS

Patient 1

The parents of this boy were referred to us for genetic counseling after his death. He was born in 1990 after 39 weeks of gestation with multiple congenital abnormalities. The family history was unremarkable. The parents were healthy and non-consanguineous. Physical examination and chest roentgenographs of the parents showed no abnormalities. In 1991 a girl was born without congenital anomalies.

The pregnancy of the affected child was complicated by polyhydramnios from the 26th week. Prenatal ultrasound showed no abnormalities. The birth weight, length, and head circumference of this boy were 3,600 g (50th centile), 51 cm (50th centile), and 35 cm (50th centile), respectively. After birth he developed respiratory distress and became cyanotic. His skin color improved after supplemental oxygen via mask. The umbilical cord pH was 7.39. Physical examination demonstrated mus-

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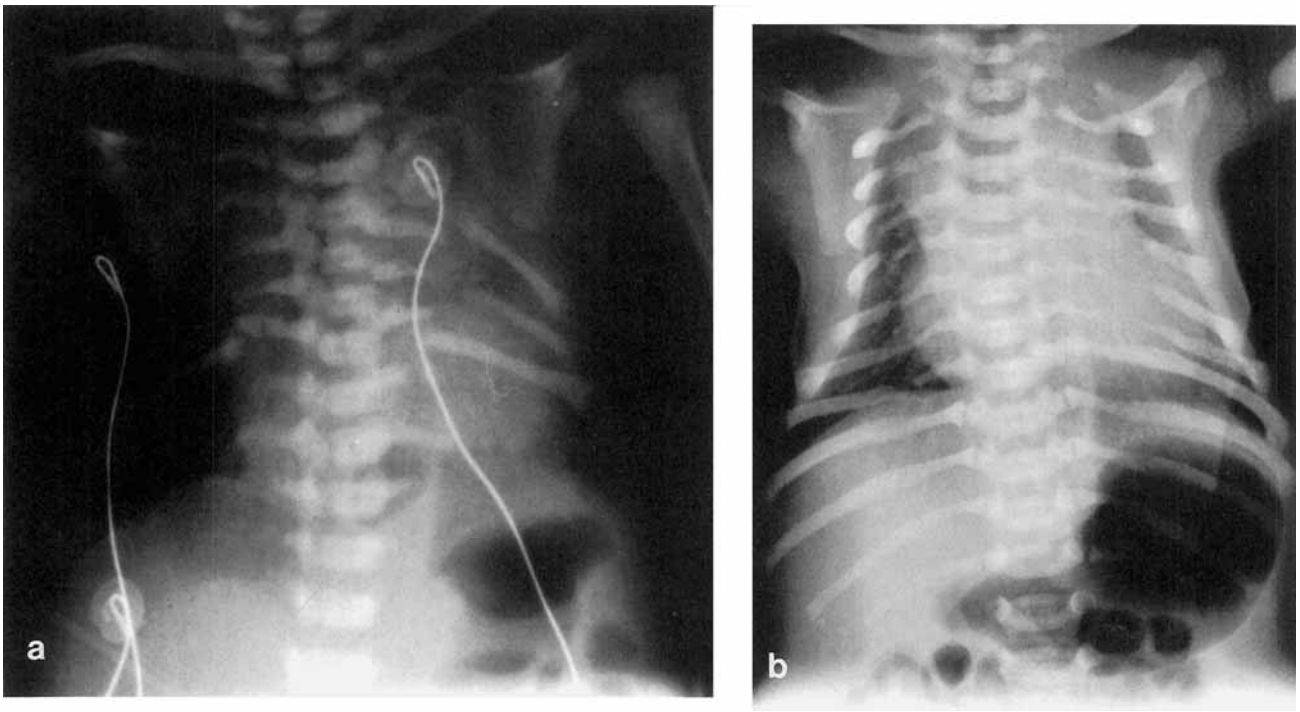

Fig. 1. Variability of the rib-gap defects on the chest roentgenographs of patient 1 and 2. **a:** Patient 1 showed marked hypoplasia of ribs 1–10, multiple posterior rib gaps, and only four ossified ribs: one on the right side and three on the left side. **b:** Patient 2 showed a bell-shaped small thorax with multiple dorsal rib-gap defects.

cular hypotonia, severe micrognathia, glossoptosis, short palate, preauricular tag, a paraumbilical fibroma, and a small and narrow thorax. The chest roentgenographs showed marked hypoplasia of the first to tenth rib, multiple posterior rib-gaps in the only four ossified ribs (Fig. 1a). No vertebral anomalies were noted except an increased intervertebral space between T4 and T5. The chromosomes were normal.

The respiratory distress increased but it was impossible to intubate the infant due to the extreme hypoplasia of the mandible. The infant died 12 hours after birth. Autopsy confirmed the multiple rib anomalies, including large unossified gaps posteriorly. Microscopic anatomy of the ossified ribs showed a normal bone and cartilage structure and no fibrous tissue. Tracheomalacia and stenosis of the left ureter was also observed. No structural cerebral anomalies were observed.

Patient 2

This boy was born in 1994 by spontaneous vaginal delivery after 39 weeks of gestation to a primiparous woman. The pregnancy was uncomplicated. There was no known exposure to teratogenic agents throughout gestation. The parents were not consanguineous and the family history was unremarkable. Birth weight and length were 2,670 g (10th centile) and 50 cm (50th centile), respectively. Head circumference was 33.2 cm (10th centile). The Apgar scores were 7 at 1, and 8 at 5 minutes. Respiratory distress, characterized by tachypnea (90 to 100/minute), sternal retractions, and cyanosis, were evident from birth. The boy was referred to our hospital because of his respiratory insufficiency and the possible need for intubation and mechanical ventilation. The initial umbilical arterial gas values on admission were pH, 7.35; pO_2, 5.8 kPa; pCO_2, 6.0 kPa;

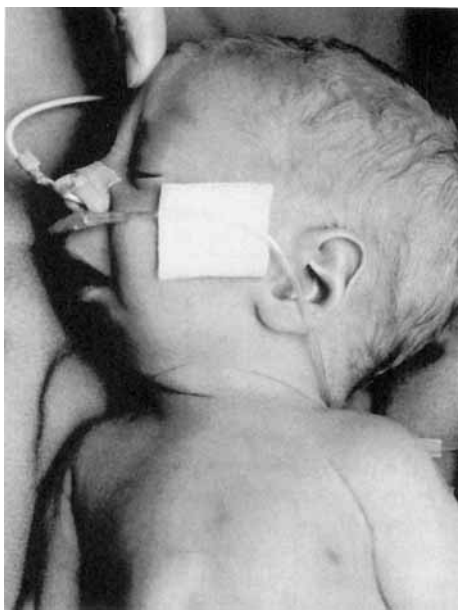

Fig. 2. Patient 2. Note severe micrognathia.

TABLE I. *Individual Characteristics of the 50 Reported Cases of CCMS**

Patient number	Sex	Age at diagnosis	Age	Gestation	Birth weight	Birth length	Head c.f.	Age parents	Respiratory distress	Micrognathia
1	M	NB	Died at 8h	40				24/24	+	+
2	M	NB	2 years	40	2,750	45.0	32.0		−	+
3	M	NB	Died at 14 days	41	2,475			33/40	+	+
4	F	NB	6 years	40	2,900			35/42	+	+
5	M	NB	Died at 52 hours	42	2,920	49.5	32.4	39/46	+	+
6	M	3 months	Died at 3 minutes	40	2,425				+	+
7	F	NB	Died at 4 days	40	2,700			32/	+	+
8		4 months							+	+
9	F	2 weeks	3 months	40	3,260			30/	+	+
10	F	1 week	Died at 10 months	40	3,325	53.0		26/31		+
11	F	NB	Died at 7 days	40	3,033			20/	+	+
12	M	11 days	5 years	40					+	+
13	F	2 days	Died at 8 weeks						+	+
14	M	10 weeks	Died at 8.5 months		2,800				+	+
15	F	1 day	Died at 9 years		2,700	44.0	34.0		+	+
16	F	11 days	Died at 50 days	36	2,820			32/32	+	+
17	M	NB	Died at 10 hours	41	3,230				+	+
18	M	14 years	14 years	40						+
19	M	NB			3,300			28/32	+	+
20	F	NB	Died at 10 days	34	1,680	38.0	30.0	26/	+	+
21	F	NB	4 years							+
22	F	13 years	13 years							+
23	M	1st day	7 months	40	2,950	48.2	35.0	27/36	+	+
24	M	7 months	9 years	34	2,400				+	+
25	F	NB	Died at 2 hours	30	1,500				+	+
26	F	22 years	24 years							+
27	F	3 years	12 years						+	+
28	M	1.5 months	Died at 6 months	40	2,300	48.2	33.2		+	+
29	M	6 months	4 years	40	3,180	54.0	35.0		+	+
30	M	NB	2 years	40	3,020	51.0	34.5			+
31	F	3 days	Died at 4 days	40	2,100				+	+
32	M	NB	Died at 34 days	36	1,100	38.5	25.0	17/	+	+
33	F	NB	Died at ?	40	3,544			33/	+	+
34										
35	M	NB	6 months	40	4,000	49.0	35.5	35/	+	+
36	F	NB	Died at 1 hour	27	700	32.0	21.5	20/27	+	+
37	M	27 years	27 years							+
38	M	NB	4 years	40	3,170	51.0	35.0	22/25	−	+
39										
40	M	NB	Died at 1 day		1,100	35.0	29.0		+	+
41	F	NB	5 weeks	36	2,500	45.5	30.5			+
42	M	NB	6 weeks	42	3,560	50.0	36.0	23/	+	+
43	M	NB	Died at 50 days	38				23/28	+	+
44	M	NB	Died at 35 days	38				23/28	+	+
45	M	NB	Died at 9 days	38				25/30	+	+
46	F	NB	2 years	38				25/30	−	+
47	M	NB	Died at ?	40	2,320	44.0	33.5	25/	+	+
48	M	NB	Died at 3 days	40	2,900			28/	+	+
49	M	NB	Died at 12 hours	40	3,600	51.0	35.0	27/27	+	+
50	M	NB	Died at 10 minutes	40	2,670	50.0	33.2		+	+

* +, present; −, absent; blank, not reported.

HCO_3 and 21.8 HCO_3 mmol/l; base excess 2.2 mmol/l (all normal values).

On physical examination severe micrognathia (Fig. 2) with glossoptosis and a cleft soft palate, a bell-shaped small thorax with slight substernal retractions were noted. The patient was in respiratory distress. Auscultation of heart and lungs was apparently normal. Chest roentgenograph showed a bell-shaped, small thorax with multiple dorsal rib-gap defects (Fig. 1b). No vertebral anomalies were observed. Additional roentgenographs of the skeletal system and skull appeared normal. Echocardiography and cranial ultrasound showed no anomalies.

The first four days of life at our hospital were uncomplicated. Initially, he needed low flow 40% oxygen but he could be weaned to room air in a few days. On the second day we started with gavage feeding and this could gradually be increased. However, on the 8th day of life, respiratory distress increased and it was necessary to perform a tracheostomy and to ventilate the patient temporarily. At 10 weeks of age the infant breathed spontaneously through the trachea cannula. Death ensued after 10 months because of obstruction of the cannula. Autopsy was not performed. Physical examination of the parents showed no anomalies.

Palatal abnormality	Glossoptosis	Posterior rib-gaps	Missing 12th rib	Microcephaly	Psychomotor retardation	Brain autopsy	Reference
		+	+			−	[Smith et al., 1966]
−	−	+	−	+	−		[Kringelbach and Henriksen, 1968]
+	+	−			−		[McNicholl et al., 1970]
+	+	+	+	+	+		[McNicholl et al., 1970]
+	+	+	+	+		+	[McNicholl et al., 1970]
+	−	+				+	[Miller et al., 1972]
+	+	+				+	[Miller et al., 1972]
		+					[Caffey, 1973]
+	+	+			−		[Nicholls and Fletcher, 1973]
+	+	+			−	−	[Langer Jr. and Herrmann, 1974]
−	+	+		+		+	[Kuhn et al., 1975]
+	+	+	−		+		[Williams and Sane, 1976]
+	+	+	+			−	[Kemperdick and Lemburg, 1976]
+	+	+		+		−	[Harris and Fellows, 1977]
+	+	+			+	−	[Harris and Fellows, 1977]
+	+	+	+	−	+	−	[Faure et al., 1978]
+	+	+	+			−	[Faure et al., 1978]
+	−	+	+		+		[Faure et al., 1978]
+	+	+	+				[Walizadeh, 1978]
+	−	+	+	+		+	[Silverman et al., 1980]
+	+	+	+	−	+		[Silverman et al., 1980]
+	−	+	+	+	+		[Silverman et al., 1980]
+	−	+		−	+		[Tachibina et al., 1980]
+	+	+		−	−		[Leroy et al., 1981]
+	−					−	[Leroy et al., 1981]
+		+		−	−		[Leroy et al., 1981]
+	+			−	−		[Leroy et al., 1981]
+	+	+			+	−	[Mohan and Mandalam, 1982]
+	+	+	−	−	−		[Hennekam et al., 1985]
−	−	−	−	−	−		[Hennekam et al., 1985]
+	−	+		−		+	[Gurgey et al., 1985]
+	−	+	+	+		−	[Clarke and Nguyen, 1985]
+	−	+		−		−	[Trautman et al., 1985]
							[Schroer and Meyre, 1985]
+	−	+	+	−	−		[Smith and Sekar, 1985]
+	+	+	+	+		−	[Merlob et al., 1987]
+	−	+	−	−	−		[Merlob et al., 1987]
+	+	+	+	−	−		[Meineke et al., 1987]
		+	+				[Feldman and Heyman, 1987]
+	+	+		+		−	[Fidalgo Alvarez et al., 1988]
−	−	+	−	−			[Burton and Oestreich, 1988]
+	−	+		−	−		[Simma et al., 1989]
+	+	+	+			−	[Drossou-Agakidou et al., 1991]
+	+	+	+			−	[Drossou-Agakidou et al., 1991]
+	+	+	+			+	[Drossou-Agakidou et al., 1991]
+	+	+	+		−		[Drossou-Agakidou et al., 1991]
+	+	+	+	−		−	[Lim and Koh, 1992]
+	+	+	−			+	[Kang et al., 1992]
+	+	+	+	−		+	Present
+	+	+	−	+		−	Present

DISCUSSION

Constant findings in CCMS are micrognathia and posterior rib-gaps between the costovertebral junction area and the lateral arc. Therefore, a chest roentgenograph is mandatory in all newborn infants with Pierre Robin anomaly or severe micrognathia and respiratory obstruction. Variability of the rib-gap defects can be considerable, as demonstrated in our two patients. The number of ribs involved varies from a few to almost all and usually both sides are involved, although not necessarily symmetrically. Rudimentary or absent ribs have also been described, in particular the absence of the 12th ribs. Our first patient had a short palate. The second patient had a U-shaped cleft palate. Palatal abnormalities are found in about 91% of CCMS patients, mostly cleft palates (67%) but also short palates (13%). Glossoptosis is found in about 66% of cases (Tables I and II). Numerous other traits with variable expression have been described in CCMS, in particular psychomotor retardation and growth retardation. Other reported findings are congenital anomalies of various organs, including tracheal cartilage, skin, skeleton, kidney, and heart (Table III). However, the incidence of these additional abnormalities is very low.

TABLE II. Summary of the 50 Reported Cases of CCMS

Sex	
Male	28/47
Female	19/47
Average	
Gestational age (weeks) (n = 37)	38.7 ± 3.1 (range from 27–42)
Birth weight (gram) (n = 34)	2675 ± 752 (range from 700–4000)
Length (cm) (n = 19)	46.2 ± 6.2 (range from 32.0–53.0)
Head circumference (cm) (n = 18)	32.2 ± 3.9 (range from 21.5–36.0)
Age at diagnosis	
Newborn	29/48
<1 week	5/48
<1 month	3/48
<1 year	6/48
>1 year	5/48 (3 years, 13 years, 14 years, 22 years, 23 years)
Respiratory distress	37/40
Characteristics	
Oral-facial	
Micrognathia	48/48
Palatal abnormalities:	42/46
Cleft palate	31/46
Short palate	6/46
High-arched	4/46
Cleft/high arched	1/46
Glossoptosis	30/45
Thorax	
Rib-gap defects	46/47
Missing 12th rib	22/31
CNS	
Microcephaly	11/28
Psychomotor retardation	
Yes	9/22 (follow-up range from 7 months to 14 years)
No	13/22 (follow-up range from 6 weeks to 27 years)
Prognosis	
Died	
<1 week	10/27
<1 month	3/27
<1 year	11/27
>1 year	1/27
Unknown	2/27
Survived	
>1 month	5/19
>1 year	14/19 (range from 2 to 27 years)

Fifty cases with CCMS, including our two patients, in 41 families have been reported. Most cases (n = 34) have been isolated cases. In only one case [Clarke and Nguyen, 1985] consanguinity was reported. Vertical transmission has been reported in two families [Leroy et al., 1981; Merlob et al., 1987] and horizontal occurrence in four [Drossou-Agakidou et al., 1991; Hennekam et al., 1985; McNicholl et al., 1970; Trautman et al., 1985]. The paucity of familial cases has made recognition of the mode of inheritance of the CCMS difficult. There is no sex predilection. Chromosome studies have been normal.

In four families affected sibs with normal parents were reported, suggesting autosomal recessive inheritance [Drossou-Agakidou et al., 1991; Hennekam et al., 1985; McNicholl et al., 1970; Trautman et al., 1985]. McNicholl et al. [1970] reported three affected sibs, one female and two males; two died due to severe respiratory distress in the neonatal period. In this family a normal male infant was born and a further pregnancy ended in a stillbirth at 6½ months; this child was not examined. In the report of Hennekam et al. [1985] the two brothers showed a remarkably variable expressivity. The oldest sib had a severe expression of the syndrome and an occult spina bifida, whereas the other sib had a mild expression of the syndrome and a skin-covered lumbar meningomyelocele. The report by Trautman et al. [1985] described CCMS in the sib of a patient reported by Silverman et al. [1980]. Both female infants died due to severe respiratory distress. Drossou-Agakidou et al. [1991] reported four sibs, two pairs of twins, with CCMS. A great variability in the manifestations of the syndrome was described. Rib involvement was mild in three patients (patient 1, 2, and 4) and the Pierre Robin anomaly was mild in one patient (patient 4). Cerebral involvement was evident in two of the patients (patient 1 and 2) who had suffered from perinatal asphyxia. From this case it is evident that there may be a discrepancy between the severity of the rib anomalies and the clinical outcome.

TABLE III. The Number of CCMS Cases With Additional Abnormalities

Skin	
Redundant skin, including pterygium colli	6
Facial	
Low-set ears	5
Double antehelix	1
Epicanthus	5
Bilateral ptosis	1
Prominent eyes	1
Hypertelorism	1
Microstomia	1
Long philtrum	1
Prominent nose	1
Low posterior hair line	2
Short neck	3
Dental abnormalities, no tooth buds	3
Indistinct speech	6
Conductive hearing loss	5
Malformation round and oval windows	2
Tracheal	
Malformed tracheal cartilages	1
Small larynx	1
Narrow trachea	1
Orthopedic	
Clinodactyly	2
Bilateral adducted thumbs	1
Displaced radial heads	1
Hyperextensible elbows	1
Partial subluxation elbow	1
Hypoplastic humerus, ulna, and radius	1
Hypoplastic clavicles, sternum, and pubic rami	1
Bilateral coxa valga	1
Internal rotation of iliac bones	1
Bilateral clubfeet	2
Rocker-bottom feet	1
Stippled epiphysis	1
Scoliosis	4
Renal	
Left renal ectopy	1
Medullary cysts kidneys	1
Heart	
Ventricular septal defect	1
Neurological	
Occult spina bifida	1
Closed lumbar meningo-myelocele	1
Lumbo-sacral spina bifida	1
Sacral dimple	2
Miscellaneous	
Cystic fibrosis	1

Parent-to-child transmission was reported in two families [Leroy et al., 1981; Merlob et al., 1987], suggesting autosomal dominant inheritance. Leroy et al. [1981] reported the fully expressed syndrome in a mother and her two children, a son and a daughter, by different fathers. The mother and the son at age 9½years showed a normal mental development, the daughter died shortly after delivery due to intractable respiratory distress. Merlob et al. [1987] described an affected father and daughter. The clinical and radiologic pictures of the father and daughter were very similar. The father also presented with a lumbo-sacral spina bifida. The father of one of the cases reported by Miller et al. and the brother of one of the cases by Harris et al. [1977] had cleft palate, which raises the question whether cleft palate can be the sole manifestation in CCMS.

Clearly, CCMS may show a variable expressivity, both in isolated cases and familial cases. Horizontal and vertical transmission in the familial cases suggest the possibility of genetic heterogeneity with autosomal recessive and autosomal dominant inheritance. However, nonpenetrance or possible germline mosaicism of an autosomal dominant gene cannot be excluded. Large pedigrees with vertical transmission are not to be expected as genetic fitness in CCMS is greatly reduced. Since the number of familial cases is too small and the variability in rib-gap defects and additional abnormalities is too large, it is impossible to allow dichotomy between possible autosomal recessive and autosomal dominant cases.

Parents of a patient who request genetic counseling should be examined for CCMS symptoms. At physical examination micrognathia, cleft palate, and a malformed elongated narrow thorax should be looked for. Chest roentgenographs should be examined for dorsal costal anomalies like pseudoarthrosis, irregular callus formation, and abnormal angulation of ribs.

The word "cerebro" implies that there is always cerebral involvement in patients with CCMS. However, so far during life in only three living patients structural cerebral anomalies have been detected by ultrasound and CT scan [Burton et al., 1988; Clarke and Nguyen, 1985; Merlob et al., 1987]. Microcephaly, a large porencephalic cyst, and no definable ventricular system or interhemispheric fissure was described by Clarke and Nguyen [1985] in their patient. Merlob et al. [1987] reported a patient whose prenatal ultrasound study showed "a fluid-filled supratentorial" compartment. The infant died approximately 1 hour after birth and this observation was not confirmed. The case of Burton et al. [1988] had agenesis of the corpus callosum, "enhancement" of the right leaf of the tentorium cerebelli, absence of the left leaf of the tentorium, and enlargement of both lateral ventricles.

Furthermore, in nine infants brain autopsy was performed [Drossou-Agakidou et al., 1991; Gürgey et al., 1985; Hennekam et al., 1985; Kuhn et al., 1975; McNicholl et al., 1970; Miller et al., 1972; Silverman et al., 1980; present case]. In six cases normal histology was found [Drossou-Agakidou et al., 1991; Hennekam et al., 1985; Kuhn et al., 1975; Miller et al., 1972; present case]. In the other three cases cerebral anomalies of variable origin were reported. McNicholl et al., [1970] reported normal gross histology but poor myelinsation. Silverman et al. [1980] reported a low brain weight, gliosis, and focal glial heterotopia in the cerebrum and cerebellum, and Gürgey et al. [1985] found dilated lateral ventricles, gliosis, and a 5th ventricle.

About ⅓–½ of the surviving infants, have psychomotor retardation (Table I and II), which may very well be secondary to perinatal and postnatal hypoxia in most cases. Almost all infants have suffered severe respiratory distress in the neonatal period due to glossoptosis secondary to micrognathia and "flail chest" secondary to the rib gap defects. Approximately 32% of the infants with CCMS died in the neonatal period and approximately 56% died within 1 year, usually due to severe respiratory distress. Unfortunately, no follow-up stud-

ies have been reported in the surviving infants with psychomotor retardation. Follow-up studies may detect similar cerebral abnormalities as in infants who suffered severe perinatal asphyxia. This may support the hypothesis that psychomotor retardation is most likely secondary induced. Meineke et al. [1987] suggested already that "costo-mandibular" syndrome might be a better designation than CCMS. Since the introduction of neonatal intensive care units, early treatment of respiratory distress may avoid hypoxemic episodes and secondary cerebral damage. Digitally assisted tracheal intubation is preferred [Sutera and Gordon, 1993] in patients with severe micrognathia and Pierre Robin anomaly as direct rigid laryngoscopic intubation may be extremely difficult to perform in these patients.

Prenatal diagnosis is very difficult to establish and probably restricted to families with a positive history for CCMS. In utero roentgenographs showed multiple rib deformities in the third affected child described by McNicholl et al. [1970]. Second trimester ultrasound showed very short and unusually shaped ribs [Merlob et al., 1987]. Variable expression of the rib defects probably precludes early prenatal detection in all cases. Assessment of mandibular growth might enhance reliability of prenatal diagnosis in at risk pregnancies.

Histological examination of the rib gaps shows fibrous tissue [Kang et al., 1992; Kringelbach and Henriksen, 1968; Miller et al., 1972]. Pre- and postnatal growth retardation are common in CCMS. One might speculate that retarded maturation of the dorsal rib anlage causes the rib gaps as these areas fail to ossify thereby causing pseudoarthrosis and chest deformity which contributes to chest deformities and respiratory failure. Similarly retarded maturation of the developing mandible might cause micrognathia and increase the chance of a cleft palate.

In conclusion, the CCMS is a very rare entity often associated with the Pierre Robin anomaly. However, if a bell-shaped, small thorax with typical rib-gap defects are present on the chest roentgenograph, CCMS can be easily diagnosed. The severity of the rib-gap defects is quite variable and variable expression is seen both in isolated and familial cases. CCMS usually occurs as an isolated event in a family. Of 41 reported families, four reports describe horizontal and two reports describe vertical transmission of CCMS. This might imply genetic heterogeneity with autosomal recessive and autosomal inheritance. Careful family studies are necessary before genetic counseling is given.

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